REMARKS

Claims 1-21 are finally rejected under 35 USC § 103 (a) as unpatentable over Hirose et al. in view of Yu et al., Tsao et al., Hackeng et al., Furuya et al. and Lemieux et al. This is a new rejection which includes Yu, et al. in addition to the previously cited references to provide support for the rejection of the claims as amended in the response dated March 12, 2010. In the March 12, 2010 response, the applicants amended the claims by requiring that the ratio of the amount of HMW adiponectin to total adiponectin or LMW adiponectin increases within four weeks of the commencement of the therapeutic treatment for insulin resistance.

The applicants traverse this rejection. The Examiner has not made a convincing case that the claims are obvious. On page 3 of the Office Action, the Examiner summarizes the applicant's arguments from the March 12, 2010, response as follows:

1) Hirose does not teach measurements of adiponectin within 4 weeks.
2) Hirose does not suggest that adiponectin is a marker for diabetes and would allow for monitoring the effectiveness of the diabetic drug ploglitazone.
3) Tsao does not teach that HMW or LMW adiponectin have different effects in diabetic patients or on diabetes.
4) Hackeng, Furuya, and Lemieux do not teach ratios of adiponectin.

The Examiner's summary of the above arguments that were previously submitted is clarified and corrected below, in view of the Examiner's subsequent arguments, as follows:

1) Hirose does not teach the measurement of HMW adiponectin, LMW adiponectin, or the ratios of HMW adiponectin to LMW or total adiponectin within 4 weeks or within any other period of time.
2) Hirose et al. does not teach that HMW adiponectin or the ratio of HMW adiponectin to LMW or total adiponectin is a marker for successful treatment of diabetes with an insulin sensitizing drug. The authors stated in the Abstract that "Serum adiponectin levels increased in all patients" in the study. In the Yu et al. reference that is cited in the current rejection, it is stated that all diabetic patients respond to treatment with an insulin

sensitizing drug by exhibiting an increase in total adiponectin, whether or not the patients respond to treatment by showing an improvement in insulin sensitivity. Thus, total adiponectin, which was measured in Hirose et al. and Yu et al., is a marker that shows that a patient has been treated with an insulin sensitizer, but it is not a marker for successful treatment of diabetes, since the responders and non-responders all showed an increase in total adiponectin. Hirose et al. do not suggest that HMW adiponectin or the ratio of HMW adiponectin to LMW or total adiponectin is a marker for successful treatment of diabetes.

3) Tsao et al. do not make any definitive statements about HMW and LMW adiponectin or their ratio as a potential biomarker for identifying responders to treatment with an insulin sensitizer There are references to other publications that are cited in Tsao et al. that mention hexameric and higher oligomers of adiponectin as perhaps having an effect on glucose production, but there is nothing in Tsao et al. or the other references that is connected with identifying diabetic patients who are responding to treatment with an insulin sensitizer. The primary focus of this publication is the effect of adiponectin oligomers on NF-κB.
4) Hackeng, Furuya, and Lemieux talk about using ratios to refine biological data, but none of these references have any connection with adiponectin oligomers. These references appear to have been chosen to support the rejection, even though there is nothing in any of the references that would lead one of ordinary skill in the art to apply similar principles for evaluating the responses of diabetic patients to treatment with insulin sensitizers.

FURTHER REMARKS ON THE CITED REFERENCES

Hirose et al. The primary reference Hirose et al. discusses a clinical study in which 10 diabetic patients were treated with the insulin sensitizer pioglitazone for three months. The authors measured total adiponectin and found that the amount of serum adiponectin increased in all of the patients. Hirose et al. stated that adiponectin would have an antiatherosclerotic effect, not an antidiabetic effect. Oligomers of adiponectin (HMW and LMW) were not measured or mentioned in the publication. Furthermore, experimental data were not measured until after three months had passed.

Yu et al. Yu et al. is cited to support the Examiner's contention that Hirose et al. and Yu et al. together disclose the use of serum adiponectin as a biomarker for treatment of diabetes over a time range of 2 weeks to 3 months. Applicants respectfully

submit that the two references do not support this contention. The abstract of Yu et al. provides a good summary of the study that was disclosed in the paper. Yu et al. disclose a study of the effects of troglitazone, another insulin sensitizing drug, on 10 diabetic and 17 non-diabetic subjects (8 lean, 9 obese). Fasting plasma glucose was reduced by the drug treatment in the diabetic patients, but not in the non-diabetic patients, after 12 weeks of treatment. No data were obtained before the expiration of 12 weeks. Baseline adiponectin levels were at a lower level in the diabetic patients before the study began than in the non-diabetic patients. Adiponectin levels increased uniformly in all of the subjects who were treated with troglitazone, whether they were diabetic or not.

The publication on page 2973, first column, near the end of the first full paragraph, states that adiponectin levels increased uniformly in all of the subjects by the end of one month of treatment. No measurements were made until one month of treatment had been completed. The authors found that adiponectin levels increased in normal rats (not humans) after two weeks of treatment (page 2972, first column). Yu et al. cited a publication by Combs et al., *Endocrinology* 143 (3): 998-1007, 2002, that discloses data in which normal human subjects showed an increase in Acrp 30 (adiponectin) after two weeks of treatment with rosiglitazone, another insulin sensitizer. Combs et al. do not mention HMW and LMW adiponectin and do not provide any suggestion that measurement of adiponectin oligomers can be used to identify responders to treatment of diabetic patients with insulin sensitizers. A copy of the Combs et al. publication is included with this response.

An interesting feature of the Yu et al. paper is the observation by the authors that three of the diabetic patients in the study were classified as non-responders to treatment with an insulin sensitizer with troglitazone, showing <10% improvement in fasting plasma glucose (page 2970, first column, lines 3-8). On page 2973, first column, last full paragraph, Yu et al. point out that the non-responders to treatment with troglitazone had an increase in adiponectin that was comparable to the increase in adiponectin in the diabetic patients who responded to treatment with troglitazone. There is clearly nothing in Yu et al. that suggests that measurement of the adiponectin oligomers would help to identify responders and non-responders to treatment with an insulin sensitizer or that would motivate one of skill in the art to consider that HMW and LMW adiponectin might be useful biomarkers. Total adiponectin is totally uninformative about whether patients are responders or non-responders

to treatment with insulin sensitizing drugs, and there is no reason to look at HMW or LMW adiponectin based on the Yu et al. publication.

Yu et al. therefore does not show or suggest that any form of adiponectin is a biomarker for whether a patient is responding to a treatment of diabetes. Diabetic and non-diabetic subjects all exhibit a uniform increase in adiponectin after treatment with troglitazone. The increase in adiponectin after treatment with troglitazone is the same for diabetic and non-diabetic subjects. The increase in adiponectin is the same for diabetic patients, whether or not they respond to the treatment for diabetes. The adiponectin is therefore not a biomarker for the successful treatment of diabetes. It is only a biomarker that shows that the subject was treated with an insulin sensitizer. The Yu et al. publication refers to adiponectin as "a convenient biomarker for drug administration" in the last paragraph of the publication on page 2973, second column. In other words, adiponectin is merely a biomarker that shows that the insulin sensitizer was administered to the subject, and provides no signal as to whether or not the subject is diabetic and whether or not a diabetic patient is responding to treatment.

In summary, Hirose et al. and Yu et al. show that adiponectin is a biomarker that shows only that a subject was treated with an insulin sensitizer. Adiponectin levels increase within two weeks. But the increase in adiponectin does not provide information on whether or not treatment of a diabetic patient with an insulin sensitizer has been or will be successful. HMW and LMW adiponectin are not mentioned in these papers, and there is no way that one of skill in the art after reading Yu et al. and Hirose et al. would conclude, or even suspect, that there might be a biomarker that will indicate whether a diabetic patient will respond to treatment with an insulin sensitizer in any time period, or that the biomarker is an oligomer of adiponectin.

Tsao et al. This is the only reference cited by the examiner that mentions the oligomers of adiponectin (HMW and LMW). Tsao et al. does not suggest that the oligomers may be useful biomarkers which will indicate whether or not a patient is a responder to treatment with an insulin sensitizer, in less than four weeks or within any other period of time.

The Tsao et al. authors state on page 29361, second column, in the paragraph entitled "Discussion," that the "major result of our study was that Acrp30 hexamer and HMW species but not Acrp30 or gAcrp30 trimers cause activation of NF-κB in C2C12

myoblasts and differentiated myotubes." However, Tsao et al. can only speculate on the biological role of NF-κB. Tsao et al. state at the top of the first column on p. 29362 that there is no published evidence of a linkage between NF-κB activation and hepatic glucose production. In the last paragraph of the Tsao et al. paper, the authors again comment on the role of adiponectin oligomers in the activation of NF-κB, but they do not in any way suggest that the adiponectin oligomers may be early biomarkers that would identify whether a patient is responding to treatment with an insulin sensitizer within four weeks of the commencement of treatment. In fact they do not comment on whether or not biomarkers might even exist that would indicate whether a patient is responding or will be a responder to treatment with an insulin sensitizer.

Yuan et al. Finally, the Examiner mentions Yuan et al. in the text of the Office Action, although he does not cite Yuan et al. in the actual rejection on page 5. The Examiner cites Yuan et al. as evidence that activation of NF-κB may be a part of the pathway in the response to anti-diabetic drugs or to an improvement in insulin resistance.

Yuan et al. states that high doses of salicylates (4-10g per day) have been used to treat inflammatory conditions, such as rheumatic fever, and that high doses of aspirin are thought to inhibit NF-κB and its upstream activator IKKβ rather than working through cycloxygenases to reduce inflammation. Yuan et al. also state that high doses of salicylates are known to lower blood glucose concentration, and Yuan et al. hypothesize that salicylates may inhibit signaling though the IKKβ pathway, which in turn might lead to improved insulin sensitivity. The suggestion that IKKβ inhibition might be a target for insulin sensitization is at best hypothetical based on the Yuan et al. publication, since it is based on the observation that high doses of aspirin treat inflammatory conditions and also lower blood glucose. These can be coincidental and unrelated effects. The statement in the Office Action at the top of page 2 that the "link between NF-κB activation and insulin resistance and diabetes has long been known" is an overstatement.

The Yuan et al. reference is unusual in the sense that it states that there may be a connection between activation of NF-κB and the treatment of diabetes. NF-κB is a receptor that was not well understood when the instant application was filed. A review article from 2001 on NF-κB signaling is included with this response: S. Aradhya and D.L. Nelson, Current Opinions in Genetics & Development 2001, 11: 300-305. The article mentions a large number of diseases, including diabetic nephropathy, that might have a connection with NF-κB but it does not mention

diabetes. There are many publications on NF-κB, but almost none of them suggest that diabetes is connected with the receptor. The suggestion by Yuan et al. that activation of NF-κB may be connected with diabetes is not persuasive as a reference for obviousness. Almost all other papers on NF-κB activation suggest otherwise. There is no obvious known connection between NF-κB activation and the treatment of diabetes.

Conclusion

The Examiner has not made a convincing case that the claims are obvious over the cited references. None of the references suggest that HMW adiponectin is a biomarker that provides information on whether a diabetic patient is responding to treatment with an insulin sensitizing compound, either within a period of four weeks or without any time limit.

It is respectfully submitted that the claims are in conditions for allowance. A Notice of Allowance is earnestly solicited.

If the Examiner wishes to discuss any matter relating to this application, he is invited to telephone the undersigned attorney.

Respectfully submitted,

By _____

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